REMARKS

Claims 27, 29-33, 44, and 47-49 are currently pending in this application. Claims 27, 29-33, 44, and 47-49 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and for lack of enablement. Claims 27, 29-33, 44, and 47-49 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 27, 29-33, 44, and 47-49 are rejected for obviousness-type double patenting over claims 1-11 of U.S. Patent No. 6,372,432. The Examiner objects to the title of the application for being insufficiently descriptive. The Examiner also objects to the specification for improper incorporation of patent and non-patent documents by reference. By this reply, Applicants cancel claim 29, amend claims 27, 44, 48, and 49, and address each of the objections and rejections. Applicants reserve the right to pursue cancelled subject matter in a divisional application.

Support for the Amendments

Support for the amendment to claims 27, 48, and 49 is found in the specification at, e.g., page 1, lines 4-9; page 3, lines 6-22; page 4, lines 15-18 and 25-30; page 7, lines 16-25; page 10, lines 5-20; page 17, lines 11-22; page 20, lines 6-14; page 21, lines 19-28; page 22, lines 1-17; page 28, lines 18-30; page 29, lines 1-31; and page 30, lines 1-5. No new matter is added by the amendment.

Objection to the Title

The Examiner objects to the title of the application because it is insufficiently descriptive of the invention. Applicants have amended to the title to more clearly describe the invention

recited in present claims 27, 29-33, 44, and 47-49. This objection can now be withdrawn.

Objection to the Specification

The Examiner objects to the specification, stating:

> The amendment filed 19 May 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure...The added material, which is not supported by the original disclosure is...[t]he insertion of a phrase into the specification at numerous locations that various documents have now been 'incorporated by reference. (Office Action, p. 2.)

In response, Applicants have amended the specification to remove the "incorporation by reference" insertions. Thus, this objection can now be withdrawn.

In addition, Applicants note that the Examiner in the present Office Action did not reiterate the objection to the specification for improper incorporation by reference of the various patent and non-patent publications discussed in the specification. Accordingly, it is Applicants understanding that this objection has been withdrawn.

Obviousness-Type Double-Patenting Rejections

Claims 27, 29-33, 44, and 47-49 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,372,432. In response to this rejection, Applicants submit a terminal disclaimer herewith, waiving the terminal portion of the term of the entire patent to be granted upon the above-identified application subsequent to the expiration date of U.S. Patent No. 6,372,432. In light of the terminal disclaimer, Applicants respectfully request that the rejection of claims 27, 29-33, 44, and 47-49 for obviousness-type double patenting be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 27, 29-33, 44, and 47-49 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner states that "[c]laims 27, 48, and 49 are indefinite with respect to what constitutes the metes and bounds of 'remote detection'" (Office Action, p. 12). Applicants respectfully disagree that the term "remote detection" is unclear, but have amended independent claims 27 and 48 to remove the term and to further clarify that the given, predefined pathological condition sought to be detected in a human subject is "a pathological condition that causes disease in a tissue distinct from blood cells of said human subject."

The specification teaches methods that can be used to detect a pathological condition in a human subject by "using biological materials distinct from the pathological tissues" (see, e.g., page 3, lines 9-11; emphasis added). The specification further teaches that

> [m]ore particularly, the present invention is based notably on the demonstration that it is possible to determine, from biological samples comprising circulating cells, the presence or the risk of development of a pathology. More particularly, the invention is based on the demonstration that it is possible to detect, in a biological sample comprising blood cells, the existence of a pathology, including at very early stages of initiation and development, for which all other existing diagnostics would be ineffective. (Specification, page 3, lines 16-22; emphasis added.)

Moreover, the specification states:

> Thus, the present invention is based firstly, on the use of blood cells in a remote test for the presence of a pathological event and, secondly, on the use of genomic methods of detection of alterations in the expression (particularly the transcription) of the genome in these cells. (Specification, page 4, lines 15-18.)

Thus, detection of the pathological condition in the subject occurs by detecting changes in the gene expression of the subject's circulating blood cells (i.e., the blood cells act as sentinel cells),

which occurs as a result of their contact with the diseased tissue. For this reason, the circulating blood cells, which are distinct from the diseased tissues, can be used to detect the pathological condition in a subject. Applicants respectfully submit that the rejection of claims 27, 29-33, 44, and 47-49 under 35 U.S.C. § 112, second paragraph, can now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 27, 29-33, 44, and 47-49 are rejected under 35 U.S.C. § 112, first paragraph, for new matter based on a lack of written description in the specification. The Examiner states that "applicant's representative asserts that support for the new limitations [in claims 27 and 47-49] can be found at page 2, lines 27-30, and at page 3, lines 9-11. A review of the cited passages fails to find support for the new claims and for the new limitations inserted into claim 27" (Office Action, pp. 5-6). Applicants respectfully disagree with the Examiner's conclusion that the specification does not support the prior amendments to claims 27 and 47-49.

The M.P.E.P. § 2163.02 makes clear that the standard for complying with the written description requirement is an objective one. The M.P.E.P. § 2163.02 states that "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" (citations omitted). For the reasons discussed below, the methods of present claims 27, 29-33, 44, and 47-49, which are fully and clearly described in the present application, satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicants' Specification Teaches Methods for Detecting Pathological Conditions in Tissues Other than Blood Using Blood Cells

Applicants were the first to recognize that a subject's circulating blood cells, in particular, lymphocytes, macrophages, monocytes and dendritic cells, can be used as a surrogate to detect the presence of a pathological condition in a tissue of that subject other than blood based on the alteration of gene expression in blood cells as a result of their contact with the diseased tissue (see, e.g., page 5, lines 1-5, of the specification). Applicants' specification fully and clearly describes this inventive contribution at, e.g., page 3, lines 16-22, of the present specification.

The Specification Discloses the Preparation of Appropriate Nucleic Acid Libraries for Any Pathological Condition

Applicants' specification also fully describes methods for preparing nucleic acid libraries specific for any given, predefined pathological condition; the nucleic acid library so prepared can then be used to detect the chosen pathological condition in a subject. The specification states that nucleic acid molecules specific to a given, predefined pathological condition can be prepared by

> (i) obtaining an initial nucleic acid preparation from a blood cell isolated from an organism presenting a pathology, (ii) obtaining a reference nucleic acid preparation from a blood cell isolated from an organism that does not present said pathology, (iii) a hybridization step between said initial preparation and the reference preparation, and recovery of the nucleic acids characteristic of the blood cell from the organism in a pathological situation. (Specification, page 8, line 29, through page 9, line 3.)

The nucleic acid molecules so recovered constitute the nucleic acid library or "bank" referred to in the specification and in present independent claims 27 and 48, and claims dependent therefrom (see, e.g., page 7, lines 11-14, and page 8, line 29), and are specific for the

given, predefined pathological condition sought to be detected.[1] Applicants point out that the present specification directs the skilled artisan to several methods that can be used to prepare the nucleic acid molecules of the nucleic acid library, including, e.g., International Application No. PCT/FR99/00547 (see, e.g., page 17, lines 11-22, of the specification), which was publicly available at the time the present application was filed.

The M.P.E.P. § 2163 states:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail...If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, the adequate description requirement is met. (Citations omitted.)

Furthermore, as was stated by the Federal Circuit in *Falkner v. Inglis* (448 F.3d 1357, 1366; 79 U.S.P.Q.2D (BNA) 1001 (Fed. Cir. 2006) (*citing LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345, 76 U.S.P.Q.2D (BNA) 1724 (Fed. Cir. 2005)), "it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. Because the present specification, when combined with the prior art and the knowledge of one skilled in the art, fully and clearly describes the nucleic acid libraries recited in present claims 27, 30-33, 44, and 47-49 and how to obtain them, Applicants submit that the requirements of 35 U.S.C. § 112, first paragraph, have been met.

Moreover, the specification teaches that nucleic acid libraries can be prepared for several

[1] Applicants also emphasize that not only do these methods produce nucleic acid molecules that are specific to the pathological condition sought to be detected, they do so without requiring any knowledge whatsoever of the sequences of these nucleic acid molecules. Thus, Applicants need not know or have described the sequences of the nucleic acid molecules of the library in order to practice the methods of present claims 27, 30-33, 44, and 47-49.

given, predefined pathological conditions. In particular, the specification teaches the preparation of nucleic acid libraries specific for pathologies that involve deregulation of cell signaling pathways or excessive cell proliferation. The specification states:

> As noted above, the process of the invention can be implemented for the detection of different types of pathologies, notably pathologies associated with deregulation of cell signalling pathways. These may be pathologies related to ageing, such as neurodegenerative disorders for example, or any other pathology involving particularly an abnormal level of cell proliferation, such as cancer, stenosis, etc. (Specification, page 7, lines 27-31; emphasis added.)

In addition,

> [t]he methods set forth by the invention more particularly comprise the constitution of nucleic acid clones and banks from RNA(s) extracted from different diseases, at different stages of their progression, and obtained from both pathological tissues and from blood cells whose genetic expression was affected by these tissues. These clones and banks are advantageously obtained by methods for differential analysis of gene expression. The differential signatures obtained are therefore specific to the differences between the healthy tissue and the diseased tissue on the one hand, and between the blood cells of the patient and the blood cells of the healthy control on the other hand. These signatures can therefore be expressed preferably in either the pathological samples or the control samples. (Specification, page 10, lines 5-14; emphasis added.)

Thus, Applicants' specification fully and clearly discloses the preparation of nucleic acid libraries specific for any pathological condition by isolating the portion(s) of expressed nucleic acid molecules (i.e., mRNA molecules) that differ between blood cells taken from a subject with the pathological disease to be detected and blood cells taken from a healthy control. The differentially expressed nucleic acid molecules are specific to the pathological condition and can be used to detect the presence of the pathological condition in a test subject. Given the full and complete disclosure in Applicants' specification for preparing nucleic acid libraries specific for any given, predefined pathological condition, Applicants respectfully submit that the written description requirement of 35 U.S.C. § 112, first paragraph, has been met for present claims 27,

30-33, 44, and 47-49.

The Specification Describes Using a Hybridization Profile to Detect a Given, Predefined Pathological Condition in a Human Subject

Following preparation of the nucleic acid library, the specification further teaches, and present independent claims 27 and 48, and claims dependent therefrom, further recite, preparing nucleic acid molecules from the blood cells of a subject to be tested for the presence of the given, predefined pathological condition and hybridizing them to the nucleic acid molecules of the nucleic acid library to obtain a hybridization profile. This step of the method is fully disclosed in the specification at, e.g., page 22, lines 1-5, which states:

> The invention allows determination of the presence of signatures specific for different disease stages by hybridizing a sample of nucleic acids from cells present in the blood circulation, with the aforementioned genetic markers, the observed hybridization profile indicating the pathophysiological deregulation in the subject from which the blood sample was taken.

As presently amended, independent claims 27 and 48, and claims dependent therefrom, further clarify that detection of the given, predefined pathological condition in a test subject occurs by correlating the subject's hybridization profile (i.e., the first hybridization profile), which is obtained by hybridizing the nucleic acid molecules derived from the blood cells of the test subject to the marker nucleic acid molecules of the nucleic acid library, with a second hybridization profile obtained using blood cells from a subject having said given, predefined pathological condition. It is the correlation of the subject's hybridization profile to the second (or positive control) hybridization profile that indicates the presence of the pathological condition in the test subject. The specification discloses the use of such a second hybridization profile on, e.g., page 29, lines 8-13 and 22-23, stating:

> The use of nucleic acid probes derived from blood cells of patients with or without the screened pathology (neurodegenerative disease, cancer, etc.) enables to screen for the existence of signatures that are present in the experimental predictive banks created from experimental disease models. The presence of common signatures constitutes a diagnosis that the individual being tested is at risk for developing such a pathology. (Emphasis added.)
>
> *****
>
> - These cDNA banks are then validated by hybridization with probes prepared from individual blood samples from patients or healthy subjects. (Emphasis added.)

Thus, the specification clearly discloses hybridizing nucleic acid molecules derived from the blood cells of patients with the given, predefined pathological condition to the nucleic acid library characteristic of a given, predefined pathological condition in order to validate the nucleic acid library and to confirm the presence of the given, predefined pathological condition in the test subject based on the hybridization profile obtained.

For all the reasons discussed above, it is respectfully submitted that the specification provides a complete written disclosure of the invention recited in present claims 27, 30-33, 44, and 47-49, such that one skilled in the art would recognize that Applicants were in possession of the invention. Because present claims 27, 30-33, 44, and 47-49 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, Applicants respectfully request withdrawal of the rejection of claims 27, 29-33, 44, and 46 for lack of written description.

Enablement

Claims 27, 29-33, 44, and 47-49 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states:

> A review of the specification fails to find where any hybridization profile has been determined for any known human pathological condition, much less one associated with a deregulation of a cell signaling pathway.

> While one is not required to teach each and every possible embodiment encompassed by the claims, the specification has not been found to teach a reproducible method whereby any specific human pathological condition could be identified. In short, applicant has not provided the essential starting materials and reaction conditions needed to practice even a part of the claims' scope. (Office Action, p. 9.)

Applicants respectfully disagree with the Examiner's conclusion that the methods of present claims 27, 30-33, 44, and 47-49 lack enablement because, for the reasons discussed below, the present specification provides all of the essential starting materials and reaction conditions needed to practice the recited methods.

Applicants have Demonstrated an Actual Reduction to Practice

Contrary to the Examiner conclusion, Applicants have done more than merely "[t]oss[] out the mere germ of an idea" (*Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2D 1001 (Fed. Cir. 1997)). Applicants have provided conclusive evidence that the methods of the present claims 27, 30-33, 44, and 47-49 work as claimed (see Declaration of Dr. Fabien Schweighoffer filed on May 17, 2006). Using the methods of present claims 27, 30-33, 44, and 47-49, which are fully and completely described in the present application, Applicants successfully generated a nucleic acid library that could be used to detect bovine spongiform encephalopathy (BSE), and then Applicants used that library to actually detect the presence of BSE in cattle that were naturally and experimentally infected with prion protein (see Paragraphs 4-8 of the Declaration). Thus, unlike the situation in *Genentech*, where the Court determined that "no one had been able to produce any human protein via cleavable fusion expression as of the application date" or even five years later (*Id.*, 108 F.3d at 1367), Applicants have provided

conclusive evidence demonstrating that the full breadth of present claims 27, 30-33, 44, and 47-49 is enabled.

The Examiner, though, states that the "declaration is not commensurate with the teachings provided in the specification...[and that] declarant is a co-inventor and statements attributed to same do not represent the opinion of a disinterested third party" (Office Action, p. 11). The M.P.E.P. § 2164.05 states that "[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art" (Emphasis in original). In the present case, the Examiner has provided no reasons why the Declaration of Dr. Schweighoffer is insufficient to demonstrate the enablement of present claims 27, 30-33, 44, and 47-49 and the Examiner has certainly not indicated why the Declaration would not be convincing to one skilled in the art.

In addition, the M.P.E.P. § 2164.05 states that "[t]he weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)." Applicants submit that, notwithstanding the fact that the declarant is a co-inventor, the Declaration of Dr. Schweighoffer provides considerable factual evidence clearly showing that the methods described in the present application can be used to prepare a nucleic acid library specific for a given, predefined pathological condition (i.e., BSE), and that the library can be used to test healthy and diseased cattle for the presence of the given, predefined pathological condition (see Paragraphs 5-8 of the Declaration). Thus, Applicants submit that the Declaration of Dr. Schweighoffer provides factual evidence demonstrating that present claims 27, 30-33, 44, and 47-49 are enabled to their full breadth; the Examiner has not addressed any of

this factual evidence. Finally, Applicants respectfully submit that the evidence provided in the Declaration is commensurate in scope with present claims 27, 30-33, 44, and 47-49, and clearly demonstrates that the specification, as filed, enables present claims 27, 30-33, 44, and 47-49. Again, the Examiner has provided no reasons to rebut this position.[2]

The Specification Provides an Enabling Disclosure for Determining a Pathological Condition in a Subject based on a Hybridization Profile

The specification provides a full and complete description of how to determine the presence of a pathological condition in a test subject based on the hybridization profile obtained by hybridizing nucleic acid molecules derived from the blood cells of a test subject and nucleic acid molecules of a nucleic acid library specific for the pathological condition to be detected. The Examiner concludes that present claims 27, 30-33, 44, and 47-49 lack enablement because Applicants' specification lacks disclosure of an actual hybridization profile, and thus, "the specification has not been found to teach a reproducible method whereby any specific human pathological condition could be identified" (Office Action, p. 9). This conclusion is in error.

Genentech Inc. v. Novo Nordisk A/S does not Support the Examiner's Position that Present Claims 27, 30-33, 44, and 47-49 are not Enabled

The Examiner analogizes the present situation to *Genentech Inc. v. Novo Nordisk A/S* (108 F.3d 1361, 42 U.S.P.Q.2D 1001 (Fed. Cir. 1997)). Applicants respectfully disagree. The issue in *Genentech* was whether Genentech's U.S. Patent No. 5,424,199 when combined with the

[2] Although the Declaratory evidence is not directed to use of the methods of present claims 27, 30-33, 44, and 47-49 in a human subject, this is not inconsistent with Applicants' conclusion that the full breadth of present claims 27, 30-33, 44, and 47-49 is enabled because the method would be performed in the same way to produce the same results in a human subject.

knowledge of a skilled artisan enabled the manufacture of human growth hormone (hGH) using cleavable fusion expression. Genentech argued that one skilled in the art would have been able to practice the claimed method without undue experimentation even if the '199 specification was limited to the "disclosure of a DNA encoding hGH...[and] prior art cleavable fusion expression techniques applied to non-human proteins" (*Id.*, 108 F.3d at 1365). Novo Nordisk argued that the knowledge of one skilled in the art would not have enabled claim 1 of the '199 patent because the prior art only recognized that "trypsin and other like enzymes were used only to digest proteins, not to specifically and precisely cleave conjugate proteins to yield intact, useful proteins" (*Id.*, 108 F.3d at 1365-1366). The Court held that the combination of the specification of the '199 patent and the knowledge of one skilled in the art did not enable the claimed method because the '199 specification only disclosed the preparation of hGH "unaccompanied by a leader sequence or other extraneous proteins" (*Id.*, 108 F.3d at 1366) and the prior art "explicitly indicates that trypsin would not be useful for the cleavable fusion expression of arginine-containing proteins such as hGH" (*Id.*, 108 F.3d at 1365). The Court was further persuaded by the fact that "no one had been able to produce any human protein via cleavable fusion expression as of the application date" (*Id.*, 108 F.3d at 1367).

Thus, unlike the situation in *Genentech*, where neither Genentech's specification nor the prior art provided a trypsin-cleavable sequence that could be combined with hGH to produce a fusion protein that could be subsequently cleaved by trypsin to produce hGH in a useful form, in both Applicants' specification and publications in the art (see International Application No. PCT/FR99/00547) provide methods that one skilled in the art can use without undue experimentation to prepare nucleic acid molecules for incorporation into nucleic acid libraries for

use in the methods of present claims 27, 30-33, 44, and 47-49. Moreover, Applicants' specification teaches that the binding of nucleic acid molecules obtained from the blood cells of a subject tested for a given, predefined pathological condition to the nucleic acid library to produce a hybridization profile reveals the presence of the pathological condition in the subject because the nucleic acid molecules of the nucleic acid library are specific to the pathological condition sought to be detected. The specification teaches:

> The invention allows determination of the presence of signatures specific for different disease stages by hybridizing a sample of nucleic acids from cells present in the blood circulation, with the aforementioned genetic markers, the observed hybridization profile indicating the pathophysiological deregulation in the subject from which the blood sample was taken. (see p. 22, lines 1-5.)

To clarify how the hybridization profile facilitates detection of the pathological condition, Applicants have amended present independent claims 27 and 48 to recite step (iv), in which the hybridization profile obtained is correlated with a second hybridization profile obtained by binding nucleic acid molecules from the blood cells of a subject known to have the given, predefined pathological condition with the nucleic acid library. As amended, present independent claims 27 and 48 provide a positive control which is used to confirm the presence of the pathological condition in the test subject based on the binding of the nucleic acid molecules to "common genetic signatures." The specification teaches that "[t]he presence of common signatures constitutes a diagnosis that the individual being tested is at risk for developing such a pathology. (Emphasis added.) Thus, contrary to the Examiner's conclusion, Applicants' specification has provided considerable guidance to the skilled artisan for detecting a pathological condition in a test subject using a hybridization profile. That Applicants have chosen to describe the hybridization profile using words rather than figures or drawings is of no

moment, as the Federal Circuit has held that "[w]hile every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention" (*Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2D 1001 (Fed. Cir. 1997)). Given the considerable disclosure present in Applicants' specification of each method step recited in present claims 27, 30-33, 44, and 47-49, which disclosure is supported by prior art publications, Applicants submit that the public has been provided with reasonable enabling detail necessary to understand and carry out the invention of present claims 27, 30-33, 44, and 47-49.

Thus, for all the reasons discussed above, the present specification enables the skilled person to practice the methods of present claims 27, 30-33, 44, and 47-49, which include the preparation of nucleic acid libraries, the isolation of nucleic acid molecules from blood samples of test subjects, hybridization between the library and test sample, and the determination, by correlating the results of the hybridization step with a positive control, whether the test subject has a given, predefined pathological condition. It is thus submitted that the specification provides all the means and methodologies to perform the invention as claimed. Because present claims 27, 30-33, 44, and 47-49 are fully enabled, withdrawal of the rejection of claims 27, 29-33, 44, and 47-49 under 35 U.S.C. § 112, first paragraph, for lack of enablement is respectfully requested.

CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office Action, following receipt by the Office of a Notice of Appeal on January 22, 2007, for two months, to and including May 22, 2007, and a check in payment of the required extension fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: May 7, 2007

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